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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,220	10/23/2006	Philip A. Beachy	JHU1980-1	7759

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,220	BEACHY ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *33-36,38-49 and 53-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32, 37, and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments of 04/16/2009 have been entered in full. Claims 33-36, 38-49, and 53-58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention Claims 1-32, 37, and 50-52 are under examination.

2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-32, and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for inducing differentiation of an embryonic stem cells or embryonic or fetal neuronal stem cells into neurons, comprising contacting a said stem cells with a Hedgehog protein and a sterol-depleting agent under conditions sufficient to decrease sterol concentrations in the cells does not reasonably provide enablement for any method for any that relies on a combination of a sterol-depleting agent and any growth or differentiation factors in the absence of a Hedgehog protein wherein the stem cells differentiate into a substantially uniform population of neurons, or wherein the stem cells are from any post-natal source. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection maintains the reasons of record set forth in the office action mailed 12/16/2008, with modifications in response to Applicants' arguments and amendments filed 04/16/2009.

5. The rejection of record asserted that the specification did not provide enablement for methods wherein the cell contacted with a Hedgehog protein and β-cyclodextrin is any cell other than an embryonic neural stem cell, or the active protein is any other than a Hedgehog protein, or the resultant substantially uniform population is uniformly any particular type of neuron other than motor neuron. Applicants' arguments and amendments filed 04/16/2009 have been found persuasive with regard to the methods being applicable to the generation of those types of neurons whose differentiation is known to involve hedgehog. Such reasoning is not persuasive with regard embodiments of the method of claim 32, wherein embryonic stem cells or neuronal stem cells are recited to differentiate into intestinal cells, pancreatic cells, lung cells, or retinal cells. Furthermore, the claims as currently amended are not limited to methods that employ embryonic or fetal cells that are known to respond to hedgehog by undergoing neuronal differentiation. Moreover, claims 20-23 do not require hedgehog.

6. The rejection of record finds that long after the instant application was filed, it remained unclear whether Shh regulates adult stem cell lineages in a manner equivalent embryonic and fetal stages, or even which cells respond to Shh signaling in adult stem cell niches (Palma *et al.*, Development, 2005 Jan;132(2):335-344 (see Abstract)). Palma *et al.* found that Shh by acts as a mitogen to promote proliferation, not differentiation, of stem cells in adult mouse brain (see Abstract). In fact, prior to the instant filing, Lai et al., (*Nature Neuroscience* **6**, 21 - 27 (2003)

Published online: 2 December 2002), disclosed that Shh directly promotes hippocampal neural progenitor cell proliferation *in vitro* and *in vivo*, and that the proliferated cells maintain their pluripotency (Figures 3-5). *In vivo*, the fraction of cells that differentiated into neurons in each case (with or without Shh) was not statistically different, indicating that Shh does not bias cells toward a neuronal lineage (p.24, left column, first full paragraph). Furthermore, Lai et al. disclose that cyclopamine dissolved in cyclodextrin inhibits Shh-induced proliferation both *in vivo* and *in vitro*, but no effects on differentiation were reported (Fig. 6; page 23, right column, 1st full paragraph). Thus, both pre- and post-filing disclosures indicate that hedgehog proteins do not promote neuronal differentiation of post-natal neural progenitors. The instant specification does not provide evidence to overturn the prevailing understanding in the art.

7. The rejection of record finds that the specification does not show any conditions wherein β-CD is sufficient to positively effect TGFβ signaling, or that BMP ever produces a substantially uniform population of neurons, as recited in claims 20-23. β-CD does not seem to alter the effect of BMP ([0115] in the specification as filed). Applicants' arguments filed 04/16/2009 did not address this point. It is further noted that neither the specification nor the prior art provides a rationale for predicting that a sterol depleting agent would effect TGFβ or BMP signaling, except indirectly as a result of a primary effect on hedgehog signaling.

8. It is not certain that uniform neuronal differentiation of the full range of stem cells encompassed by the claims can be achieved regardless of how much experimentation a skilled artisan might be willing to perform. Further, as stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more

than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-5, 7-9, 14-17, 20, 21, 24, 31 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Lai et al., (*Nature Neuroscience* **6**, 21-27 (2002) Published online: 2 December 2002). Lai et al. disclose that cyclopamine dissolved in cyclodextrin inhibits Shh-induced proliferation both *in vivo* and *in vitro* (Fig. 6; page 23, right column, 1st full paragraph). The controlled experiments included tests of the effect of the vehicle (cyclodextrin) on Shh-induced proliferation. Therefore, Lai et al. performed all the positively recited steps of the instant claims, which require only that a neuronal stem cell is contacted with a Hedgehog protein and β-CD.

11. Preamble language in claims of patents directed to administration of a drug are expressions of purpose and intended result, and as such are non-limiting, since language does not result in manipulative difference in steps of claims. See *Bristol-Myers Squibb Co. v. Ben Venue Labs Inc*., 246 F.3d 1368, 58 USPQ2d 1508 (Fed. Cir. 2001) (61 PTCJ 623, 4/27/01), where a patent for administering the anti-cancer drug paclitaxel was anticipated by a scientific article describing the same method but with no anti-tumor response. That court held that expressions of anti-tumor efficacy did not distinguish the claimed method from the prior art. The court further held that preamble language in claims of patents directed to administration of anticancer drug are expressions of purpose and intended result, and as such are non-limiting, since language does not result in manipulative difference in steps of claims. Expressions of efficacy in claims of patents directed to administration of anticancer drug will not be given limiting effect, even though new uses of old processes are patentable, since claimed process in present case is not directed to new use, and it consists of same steps described in prior art reference, and since newly discovered results of known processes directed to same purpose are inherent, and thus are not patentable. Therefore in the instant case, Applicant's assertions of intended results ("inducing differentiation of a stem cell into a neuron"; "alter the responsiveness of a stem cell to a Hedgehog signal") do not distinguish the claimed method over prior art that teaches administration of the same agents to the same target cells. Likewise, the expressions such as "conditions sufficient to decrease sterol concentration in the cell", "thereby inducing the stem cell to differentiate into a neuron", "wherein the population of stem cells differentiate into a substantially uniform population of differentiated neurons" does not distinguish over the art because they simply reiterate the

intended result set forth in the preamble or they recite effects that would be inherent to a process step positively recited (MPEP 2111.04).

12. Claim 37 is rejected under 35 U.S.C. 102(b) as being anticipated by Hanson et al., Developmental Brain Research, 3:529-545, 1982. Hanson et al. teach the preparation of highly purified cultures of neurons from cerebral hemispheres, optic lobes, and dorsal root ganglia of 10-12-day chick embryos (see Summary, page 529). Claim 37 is drawn to a substantially uniform population of differentiated neurons produced by differentiation of embryonic stem cells or neuronal stem cells. The cultures disclosed by Hanson et al. are indistinguishable from the population recited in claim 37, as they each consist primarily of differentiated neurons. The courts have established that if a claimed product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe.,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir.1983).

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647